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ADP011046

TITLE: Malaria Chemoprophylaxis in Military Aircrew

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TITLE: Medication for Military Aircrew: Current Use, Issues, and Strategies for Expanded Options [les medicaments pour les equipages militaires: Consommation actuelle, questions et strategies pour des options elargies]

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Malaria Chemoprophylaxis in Military Aircrrew

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RESUME

La prophylaxie du paludisme chez les membres du personnel navigant militaire est une préoccupation majeure du médecin de l'air. L'article aborde les aspects aéromédicaux de la question en examinant les indications et les effets secondaires des principales molécules utilisables en prophylaxie palustre. La possibilité d'apparition d'effets secondaires neurosensoriels lors de l'emploi de certaines molécules est un critère essentiel dictant le choix final de la prescription. Les connaissances sur la chimioprophylaxie du paludisme à plasmodium falciparum étant évolutives, les règles de prescription sont susceptibles d'être adaptées ultérieurement. Dans tous les cas, la chimioprophylaxie doit s'intégrer dans une stratégie de gestion globale, comportant la mise en place de mesures antiparasitaires individuelles et collectives.

SUMMARY

Malaria prophylaxis of aircrew is one of the more frequent problems with which a flight surgeon has to cope. This article examines the aeromedical aspects of the topic by reviewing the indications and side effects of the available chemoprophylactic drugs. A potential for neurosensory side effects constitutes the most frequent reason to reject the use of a particular drug. Knowledge about malaria prophylaxis is in a constant state of change; thus, recommendations are liable to become rapidly outmoded. Whatever the chosen drug, chemoprophylaxis should always be integrated into a global management strategy which includes antivector measures on an individual and collective scale.

I. INTRODUCTION

Malaria is the most common parasitic disease around the world. According to the World Health Organisation (WHO), it is responsible for 300 to 500 million cases per year, as well as 2 million deaths.¹³

Historically, the combination of malaria with military operations has resulted in disastrous losses of personnel. The global management of this biological hazard by US forces during the Pacific campaign of World War II is widely accepted as one of the decisive factors leading to the Allied victory in those infested areas. Loss or unavailability of such highly qualified personnel as aircrew is particularly unacceptable, and thus it is imperative to determine the best way to prevent the disease.

Epidemiologic data indicate that, between 1993 and 1998, French Air Force aircrew and ground crew deployed to endemic areas experienced an annual malarial attack rate of 6.2%. In 1998, the entire French forces reported 562 malaria attacks, with unfortunately one death recorded, after an average rate of exposure of 12,350 personnel per year. Sick personnel were medically unfit for a mean time of 6.8 days. The majority of cases (77.4%) have begun overseas, while the remainder occurred following their return to France. Military personnel involved in rapid and frequent deployment are more likely to contract malaria than are those who permanently reside overseas (relative risk 5.6). The following statistics clearly show that the struggle against this parasitic disease is actually becoming more difficult as time goes by:

- 53% of malaria attacks have occurred after a stay in WHO group 3 countries (i.e., high risk of resistance), versus 47% for group 2 countries;
- although 16% of personnel display poor compliance with chemoprophylaxis as assessed by plasma drug concentration, 50% of cases have occurred among people who were taking chemoprophylaxis regularly; and
- resistance of *Plasmodium falciparum* to antimalarials, although still clearly dependent on geographic location, is spreading.

While treatment of a malarial episode is more or less established, the most logical defense continues to be prophylaxis, including disinsection, the use of repellents to avoid *Anopheles* bites, and the use of chemoprophylactic drugs.^{8,19}

The choice of adequate chemoprophylaxis relies on many criteria^{5,6,8,16,21,24,25,43,47,48} and each one should be taken into account:

- the species of *Plasmodium* potentially encountered;
- the level of awareness/education of aircrew about this infectious hazard, including the risk, the absolute need for a medical examination in case of symptoms during and after exposure, and the potential failure of the chemoprophylactic agent;
- the assessment of the risk of infection according to the country, the season, the duration and the type of the stay, and the measures locally applied to fight the biological vector;
- the current state of resistance to antimalarial drugs encountered in the country, which is available in the annually updated WHO guidelines;³³
- the practicability of the prophylactic regimen, which partly determines compliance; and
- the ease and the availability of self-treatment in case of suspicious symptoms.

An issue of particular interest to the flight surgeon is the potential side effect profile associated with the drug, particularly those adverse effects which may impair flight safety.

The main goal of this review is not to investigate the different antimalarial therapeutic drugs, or the practical measures undertaken to combat the biological vector. Rather, we will focus our

interest on chemoprophylactic drugs. When discussing the indication, we will refer to the WHO classification for countries:

- Group 1: no resistance described in the considered country,
- Group 2: resistance described but still uncommon,
- Group 3: high risk of resistance.

The chemoprophylaxis policy of each nation participating in the Working Group will not be discussed. The reader may look for this information in the database built up by the Working Group and presented in this volume.

II. THE AVAILABLE PROPHYLACTIC DRUGS

Chloroquine (Nivaquine®)

Mechanism of action: This amino-4- quinoline is directly schizonticidal. The parasite accumulates the drug inside its digestive vacuoles, which stops the enzymatic degradation of hemoglobin, the main source of amino acids for the parasite. Resistance appears when the parasite is no longer able to accumulate the drug inside the vacuoles.^{5,23}

Formulation: 100-300 mg tablets

Half-life (serum): 10-30 days

Chloroquine has a high affinity for pigmented tissue, where it is readily stored.

Range of dose:

- 100 mg per day, from the day before departure to 4 weeks following return from an endemic area
- alternate regimens are 300 mg per week, or 300 mg two times per week

Indication: Chloroquine is currently restricted to countries where chloroquine resistance has not yet been recorded (WHO Group I).

Side effects: According to many publications,^{5,8,21,36,48} side effects are usually benign and rare during prophylaxis. Nevertheless, Steffen⁴⁶ found that side effects occurred in 19.9 to 22.2 % of a group of 12,272 travelers using 300 to 600 mg chloroquine per week, including two cases of psychosis. Neuropsychologic disorders, though

unusual, have included toxic psychoses, episodes of disorientation, hallucination, impaired consciousness, and seizures. Other commonly described symptoms include headache, digestive troubles, (nausea, diarrhea), pruritus (especially in dark-skinned races), lichenoid cutaneous eruption, vertigo, and deafness.

Ophthalmologic complications are of particular interest in the aviation environment. Accommodation problems and corneal deposits have been described with chloroquine; they may disappear after the drug has been discontinued. The side effect of most concern is the development of retinopathy. According to Easterbrook,^{15,35} the visual prognosis of this retinopathy is excellent if the diagnosis is made at an early stage of the disease. The retinopathy develops in several stages,¹⁷ with dyschromatopsia, loss of visual acuity, emeralopy, and maculopathy, with an "ox eye" aspect on angiography. Retinopathy has been described among patients treated with high doses of chloroquine or hydroxychloroquine for connective tissue diseases,²² as well as among chloroquine abusers.²⁹ The greatest risk appears to be among those who were not under medical surveillance.

Retinopathy may appear with a cumulated dose of 100 g, but is more common at higher doses (300 g). The size of the daily dose is also important; daily doses should not exceed 250 mg, or 4 mg/kg/day. In a recent study, Levy et al.²⁷ argued that an ophthalmological survey was not necessary if the daily dose of hydroxychloroquine did not exceed 6.5 mg/kg. However, it should be noted that chloroquine may be more likely to cause retinopathy than hydroxychloroquine.⁴⁵ The maximal safe dose, daily or total, of chloroquine is still under debate; the main factor accounting for the differences between studies is probably the variation of retinal sensitivity to chloroquine between individuals.

In the French aeromedical experience, even in aircrew on the recommended dose of 100 mg per day, regular ophthalmologic evaluation is performed; this basic survey includes measurement of the visual acuity and color vision testing. Those parameters are recorded regularly during the career of a pilot. If necessary, determination of the contrast sensitivity curve, an automated visual field, funduscopy, and an electroretinogram could be performed. Despite the fact that none of the commonly used tests

alone is satisfactory for detecting retinopathy, Ruiz et al.³⁷ have argued for a lesser survey, using a careful corneal examination, color vision testing, visual fields, and an Amsler grid test every 9 or 12 months.

During prophylaxis with chloroquine, the occurrence of retinopathy is distinctly unusual, with twelve cases recorded by French authors.²¹ All of these patients had taken a total estimated dose of 360 g to 1300 g over many years. Since 1982, not a single case of retinopathy has been detected by the French Aeromedical Centers in aircrew taking frequent prophylactic courses of chloroquine (Corbé C., personal communication).

Cardiac toxicity may appear with accidental high doses. Voluntary poisoning with chloroquine carries a grim prognosis.

Amodiaquine (Flavoquine®)^{7,10,36,48}

The use of this drug is no longer recommended because of the risk of toxic hepatitis and agranulocytosis.

Mefloquine (Lariam®)^{4,5,7,8,16,23,25,36,40,41,48,49}

This aminoalcohol drug is closely related chemically to the amino-4-quinolines. It is schizonticidal for each type of *Plasmodium*. The site of action is the membrane of the erythrocyte; it has no effect on intrahepatocytic parasites.

Resistance to mefloquine was first described in Thailand in 1989, and is spreading. Failure of chemoprophylaxis has also been reported in Africa, but it remains rare on that continent. Resistant cases are the exception in other areas.

Formulation: 50 and 250 mg tablets

Range of dose: 250 mg per week, from 7-10 days before departure to 3-4 weeks after return

Indication: chemoprophylaxis for group 3 countries, if the length of stay is less than 3 months

Contraindication: previous history of seizure or psychiatric disorders

Side effects: Steffen⁴⁶ found a rate of side effects of 22.3% in 5342 travelers taking mefloquine for chemoprophylaxis. Usually the prevalence of side

effects varies from 15 to 40 % between studies. The following symptoms have been described and some of them are clearly of interest to aviation:

- digestive disorders (nausea, vomiting, diarrhea, abdominal pain syndrome)
- anorexia, asthenia
- pruritus
- headaches, seizure, sleep disorders²⁸
- vertigo
- psychomotor coordination troubles, spatial disorientation
- transient memory failure³¹
- psychiatric disorders,¹¹ hallucination and depressive syndromes

Neurosensory and psychiatric side effects have been described, especially with the therapeutic use of mefloquine.³⁴ Bernard, Gourbat, et al⁷ have reported a 39% rate of side effects with therapeutic doses of mefloquine. This study recorded three cases of encephalopathy with seizure; of note, seizures may be delayed. With the prophylactic use of mefloquine, the rate of frank psychiatric manifestations has been estimated at 1 per 15,000 to 20,000 (50); 90% of these side effects appear during the first 5 weeks.³⁴

The aeromedical suitability of chemoprophylaxis with mefloquine has been discussed in some articles. According to Schlagenhauf³⁸ and Steffen,^{46,47} the occurrence of side effects differs little between mefloquine and the chloroquine/proguanil combination. This may lead some to reconsider the use of mefloquine for aircrew. A study conducted with Swissair pilots⁴⁰ did not show a significant difference in performance between mefloquine and placebo. Shamiss⁴¹ has compared the suitability of mefloquine versus doxycycline in Israeli aircrews sent to Rwanda. He recorded side effects in 13% of those on mefloquine, compared with 39% of those on doxycycline. Twenty-five percent of aircrew members on doxycycline discontinued chemoprophylaxis, compared to none using mefloquine. The author concluded that mefloquine was suitable for aeromedical use because of better tolerance and compliance.

Dutch authors²⁰ have used mefloquine in Cambodia; careful survey, including clinical examination, biological analysis and regular EKG

to measure QT-intervals did not uncover any problems. During a controlled study of 95 volunteers, British experimenters¹⁴ did not observe a significant difference between mefloquine and placebo in neurologic symptoms or on neuropsychological testing.

Against this, Barrett⁴ reported a 0.7% rate of neuropsychiatric disorders with mefloquine, compared to 0.09% with the chloroquine/proguanil combination. Another study³⁹ documented an 11% rate of significant side effects related to chemoprophylaxis with mefloquine.

One particular study has emphasized the fact that the use of mefloquine increases the risk of post-malaria neurological symptoms. According to these authors,³⁰ mefloquine should not be used after previous treatment of a severe malaria attack.

Although mefloquine has been considered capable of inducing serious side effects, recent studies comparing this compound to chloroquine/proguanil^{9,12} do not seem to confirm a more serious side effect profile than standard therapy. Whether mefloquine will prove to be useful in the future remains to be seen. At the present time, most NATO countries forbid the use of this drug for prophylaxing aircrew.

Sulfonamides: *Sulfadoxine, Dapsone (Disulone®)*²³

Mechanism of action: These antifolic drugs inhibit dihydropteroate synthetase, crucial to the biosynthesis, from paraminobenzoic acid, of a metabolite essential for the parasite's growth.

Sulfonamides have no action on the gametocyte or the pre-erythrocyte form of the parasite. They are moderately active on the trophozoites and on the schizonts. They may potentiate the action of antifolinic drugs.

There is general agreement that sulfonamides should not be used as monotherapy, either for treatment or prophylaxis.

Pyrimethamine: *Daraprim®, Malocide®*²³

Those antifolinic compounds have a schizonticidal action mediated by the inhibition of dihydrofolate reductase.

Resistance, which has now been widely documented, precludes their use separately from other drugs. The level of resistance is particularly high in Southeast Asia, in the Amazon basin, and in East Africa. Pyrimethamine is still effective in West Africa.

Side effects are primarily those of folic acid deficiency, including macrocytic anemia, aphthous ulcers, and stomatitis.

Proguanil: Paludrine®²³

Its active metabolite is cycloguanil, an antifolinic drug. The mechanism of its schizonticidal action is identical to pyrimethamine.

Proguanil is no longer used separately because resistance, though less frequent than with pyrimethamine, is still a significant risk. Cross-resistance between pyrimethamine and proguanil has also been described.

Formulation: 100 mg tablet

Side effects:

- aphthous ulcers, stomatitis
- moderate digestive disorders
- alopecia
- pruritus, cutaneous eruption, depigmentation

Sulfadoxine and Pyrimethamine: Fansidar®^{7,48}

This chemoprophylactic agent has been largely discarded because of the risk of serious side effects, including Lyell syndrome, Stevens-Johnson syndrome, and agranulocytosis.

Dapsone and Pyrimethamine: Maloprim®⁴⁸

For reasons similar to Fansidar®, this combination is no longer used.

Chloroquine and Proguanil: Savarine®^{1,8,43,48}

This schizonticidal combination was previously taken as separate tablets. Several years ago, the French Army Health Service developed a new formulation, combining 200 mg of chloroquine and 100 mg of proguanil, to aid in compliance. It has been widely used by French military personnel, including aircrew, in Africa. This

formulation is now available for civilian use under the commercial name "Savarine®".

Range of dose: 1 tablet per day, from the day before departure to 4 weeks after return.

Indication:

- Chemoprophylaxis for WHO Group II endemic areas.
- Chemoprophylaxis for WHO Group III endemic areas when mefloquine is not indicated or poorly tolerated, or when the length of stay is over 3 months.

Side effects: Side effects of the two parent drugs have been described previously.

According to the French Aeromedical Center's experience, chloroquine plus proguanil has been commonly given to military or civilian aircrews. Even after repetitive use, side effects have been no more significant than those seen with chloroquine alone.

Doxycycline^{5,8,23}

This antibiotic of the tetracycline group has a schizonticidal effect on *Plasmodium falciparum* by inhibiting the biosynthesis of the 70 S ribosomal protein. It is effective on either the intraerythrocytic or the intrahepatocytic form of the parasite. Until recently, resistance to doxycycline did not seem to have appeared.

Formulation: 100 mg tablet

Range of dose: 1 tablet per day, from the day before departure to 4 weeks after returning.

Indications: Usage currently recommended for particular geographic areas.

- forest areas between Thailand and Cambodia, and between Thailand and Myanmar
- WHO Group III endemic areas in Southeast Asia when mefloquine is poorly tolerated

Side effects:

- digestive disorders (nausea, epigastric distress, vomiting, diarrhea, abdominal pain syndrome)
- photosensitization
- vaginal candidiasis
- asthenia

During the previously cited trial with Israeli aircrews in Rwanda,⁴¹ doxycycline prophylaxis was associated with worse compliance than mefloquine (75% vs 100%), as well as a higher rate of side effects (39% vs 13%). The majority of recorded side effects were digestive symptoms.

Doxycycline has been more effective than Savarine® in preventing *Plasmodium falciparum* malaria in French soldiers stationed in central Africa and in Cambodia.^{3,32}

Primaquine^{5,8,36,51}

This amino-8-quinoline may destroy the gametocyte, the pre-erythrocyte, and the intrahepatocytic form of the parasite, including the hypnozoite responsible for late relapses.

Range of dosage:

- 15 mg per day until 2 weeks following return, or
- 45 mg per week for two months following return.

Indications: Primaquine can be used to prevent infection by *Plasmodium vivax* and *Plasmodium ovale*, both of which can induce late relapse. Primaquine may be combined with chloroquine. Two randomised studies have demonstrated its efficacy (94%) in non-immune travellers as a prophylactic drug for *Plasmodium falciparum* in Java and Columbia.^{18,44}

Contraindication: The presence of glucose-6-phosphate dehydrogenase deficiency is an absolute contraindication because of the risk of hemolytic anemia. This defect is known to affect 10% of African-Americans.

Side effects:

- various digestive disorders (especially nausea)
- headache
- accommodation disorders
- agranulocytosis, anemia and methemoglobinemia

Drugs For The Future

Numerous drugs are currently under study for treatment of malaria, but relatively few studies are designed to address prophylaxis. Artemether

(Paluther®), pyronaridine, and benflumentol¹ are presently under study for such a purpose.

Azithromycin^{2,8} has emerged as a possible chemoprophylactic drug. At a dose of 250 mg per day or 1000 mg per week, it is effective on intrahepatocytic parasites, but it seems less protective than doxycycline.

Atovaquone^{1,8,23} displays a unique mechanism of action by inhibiting the mitochondrial respiration of the parasite. Thus, it is active against all four species of *Plasmodium*. A synergistic action with proguanil has been shown, while an antagonistic action with quinoline compounds has been reported. Atovaquone cannot be used alone because of the risk of emerging resistance. Malarone® combines atovaquone (250 mg) with proguanil (100 mg). Its therapeutic action has been demonstrated on *Plasmodium falciparum*, but a prophylactic action has not been demonstrated for non-immune people. For immune people, two studies^{26,42} from Kenya and Gabon have shown this combination to be effective and well tolerated despite several digestive side effects.

Other new drugs¹ are currently under study (partly at the Walter Reed Institute in Washington):

- WR 250417 is chemically close to proguanil.
- WR 99210 inhibits dihydrofolate transferase.
- WR 238605 (etaquine) and WR 182393 belong to the amino-8-quinoline family; they seem to be active on the intrahepatic form of the parasite.
- docetaxel (Taxotere®)
- inhibitors of *Plasmodium* proteins.
- inhibitors of *Plasmodium* lipid metabolism.

Some drugs appear to be capable of restoring sensitivity to chloroquine. Verapamil and an investigational compound (WR 268954) have shown such a property.

CONCLUSION

The choice of malaria chemoprophylaxis for aircrew should be seen as one of many steps towards a global management strategy for this biological hazard. The flight surgeon has in fact several different tasks to perform:

- to assess risk case by case;
- to make aircrew aware of the disease, by giving them clear and updated information during repeated briefings;
- to choose a prophylactic agent with the least deleterious side effects, keeping in mind that compliance with the drug should be optimal;
- to encourage aircrew to use physical and chemical barriers to vectors;
- to watch over the personnel he is responsible for during and after the stay; and
- to report problems with tolerance or efficacy.

Standby treatment, i.e., use of an antimalarial drug as therapy in case of suspicious symptoms, is another alternative. It could be used when aircrew are involved in frequent but short stays in endemic areas, as is often the case with civilian long-haul crews; such a circumstance which might otherwise call for almost continuous chemoprophylaxis.

Any prophylactic drug may induce side effects. The decision to use a malaria chemoprophylactic agent in military aircrew will be the result of a complex compromise between the expected efficacy and the potential for deleterious effects on flight safety. The avoidance of drugs with neurosensory side effects and of new, inadequately tested drugs seems to be the basic rule. In fact, the flight surgeon will have to choose between two different type of risks, the risk of ineffective prophylaxis, and the risk of a drug-induced mishap. A good knowledge of the available drugs, access to updated information, and rational judgment will help him to determine the most acceptable risk.

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